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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,292	12/01/2003	Juan Armendariz Borunda	061537-0036US	4513

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/724,292	ARMENDARIZ BORUNDA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-1-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-14-10 has been entered.

Applicant's amendment filed 2-14-10 has been entered. Claims 22 and 24 have been amended. Claims 28-30 and 32-34 have been canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the adenoviral vector comprises an adenoviral vector selected from the group consisting of the vector contained in ATCC Deposit No. PTA-10532" in claim 22 is vague and renders the claim indefinite. The term "comprises" is an open language that means some other component is intended other than the recited component. It is unclear what other component, such as adenoviral vector, is intended in the claim other than the selected adenoviral vector. Further, there is no description of what is contained in the ATCC Deposit No. PTA-10532. The submitted letter from ATCC only reveals that 25 vials are contained in the PTA-

10532, however, it is unclear what kind of material or adenoviral vector is contained in those 25 vials. Claim 24 depends from claim 22 but fails to clarify the indefiniteness.

4. Claim 24 recites the limitation "the therapeutic protein" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claim 24 depends from claim 22 but claim 22 fails to recite any therapeutic protein.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary

experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 22 and 24 are directed to a composition **to treat hepatic fibrosis in a human** comprising a therapeutically effective amount of unitary doses of viral particles of a recombinant adenoviral vector, wherein said adenoviral vector comprises an adenoviral vector selected from the group consisting of the vector contained in ATCC Deposit No. PTA-10532, and a pharmaceutically compatible carrier, and a method of treating fibrotic disorders in a human patient by delivering the composition by an intravenous administrative route to a liver, and expressing the therapeutic protein in the liver to treat the hepatic fibrotic disorders.

The specification discloses that the rat models, including healthy rats, rats intoxicated with carbon tetrachloride (CCl4) and rats with ligation of the bile duct (LCB), receive infusion of Ad5gal vector by iliac vein shows that the main target organ of the infused adenoviral vector is the liver. The spleen and the lung present a transduction grade lower than 1% and other organs, such as kidney, heart and brain, show no transduction at all (specification, pages 12-16).

Claim 22 recites a composition **to treat hepatic fibrosis in a human** and claim 24 reads on a method of treating fibrotic disorders in a human patient. It is apparent that intended use of

the composition of claim 22 is to treat hepatic fibrosis in a human. Thus, the claims read on gene therapy for the treatment of various fibrotic disorders in vivo.

As discussed above, it is unclear what kind of material or adenoviral vector is contained in the ATCC Deposit No. PTA-10532, therefore, it is assumed that the recombinant adenoviral vector expresses a therapeutic protein. The claims encompass treating various fibrotic disorders, such as hepatic fibrosis, renal fibrosis, pulmonary fibrosis, hypertrophic scars and keloid of the skin, and fibrosis in other target organs, in a human patient by delivering a recombinant adenoviral vector expressing a therapeutic protein under the control of a promoter to liver via intravenous administration in vivo. The specification fails to provide adequate guidance and evidence for delivering a recombinant adenoviral vector expressing any therapeutic protein under the control of a promoter via intravenous administration in vivo such that sufficient therapeutic protein can be obtained so as to provide therapeutic effects in target organs for treating any fibrotic disorder, such as hepatic fibrosis, in a human patient.

The claims read on gene transfer and gene therapy in vivo. The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain, M., 1998 (Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known

in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3). The adenoviral vector can induce both cell-killing "cellular" immune response and the antibody-producing "humoral" immune response from the host. The virally infected cells can be killed by cytotoxic T lymphocytes and the humoral response results in the generation of antibodies against adenoviral proteins. "There are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression" (e.g. p. 241, left and middle column).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors complicate in vivo gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by

the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

The claims also encompass using nucleotide sequences encoding various therapeutic proteins for treating various fibrotic diseases or disorders in a patient. However, different therapeutic proteins have different amino acid sequences and their biological functions would differ. The specification fails to provide adequate guidance and evidence for whether the claimed therapeutic protein would be able to treat various fibrotic diseases or disorders, such a hepatic fibrosis, in vivo. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the

multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Tomasinsig et al., 2005 (Current Protein and Peptide Science, Vol. 6, p. 23-34) reports that cathelicidins family proteins contain a diverse C-terminal antimicrobial domain connected to a conserved cathelicin-like N-terminal domain (the propiece) of approximately 100 residues. Cathelicidin peptides are considerably diverse in length, amino acid sequence and structure, and they have distinct functions and a diverse spectrum of activity and/or antimicrobial potency (e.g. abstract, p. 23, right column).

Smallwood et al., 2002 (Virology, Vol. 304, p. 135-145) generates several mutation at domains II and III of Sendai virus L protein and in vitro transcription and replication analysis shows that most of the mutations completely inactivate the L protein for all aspects of RNA synthesis, however, some mutations show different phenotypes from inactivation to partial activities depending on the nature of the amino acid that was substituted. "Two mutants, K543R and K666V, could synthesize some leader RNA, but were defective in mRNA synthesis and replication. K666R and G737E had significantly reduced replication compared to transcription in vitro, but replicate genome RNA much more efficiently in vivo. K666A gave transcription, but no replication." (e.g. abstract). Chattopadhyay et al., 2004 (Virus Research, Vol. 99, p. 139-145) generates mutations at each amino acid in the conserved GDNQ motif of the L protein of

Rinderpest virus and demonstrates that Q775E and Q775N mutants have about 33-42% activity of wt L protein and mutants D773E, N774A, N774D and N774Q do not support RNA synthesis at all (e.g. abstract, p. 143, left column, section 3.3). It is apparent that a single amino acid substitution and the nature of the amino acid can alter and determine the biological function of the L protein of a negative-strand RNA virus.

Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention, even same family proteins having conserved region can show diverse biological functions, and a single amino acid substitution and the nature of the amino acid can alter and determine the biological function of a protein. The specification fails to provide adequate guidance and evidence for whether the claimed adenoviral vector expressing a therapeutic protein would be able to provide therapeutic effect via intravenous administration in vivo so as to treat various fibrotic disorders, such as hepatic fibrosis. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed adenoviral vector to treat various fibrotic disorders in vivo.

In view of the unpredictable nature of gene therapy in vivo, the limitation of using adenoviral vectors in gene delivery, and the unpredictable biological function of a protein from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the recombinant adenoviral vector expressing a therapeutic protein for treating various fibrotic disorders, such as hepatic fibrosis, in a human via intravenous administration routes in vivo. One of skilled in the art would require trial and error experimentation to determine the biological function of various therapeutic proteins, preparation of adenoviral vectors expressing various therapeutic proteins, administration of said viral vectors into a subject

via intravenous administration, trial and error experimentation to determine whether sufficient therapeutic protein is expressed at the target organ via intravenous administration, and trial and error experimentation to determine whether the expressed therapeutic protein can provide therapeutic effect for treating various fibrotic disorders, such as hepatic fibrosis in a human.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Shin-Lin Chen/
Primary Examiner, Art Unit 1632